REMARKS

The Applicants acknowledge the Examiner's comprehensive Office Action with appreciation. Claims 1-21 remain under consideration. The Examiner's acknowledgement of the PCT basis for this application is appreciated.

The Examiner has objected to the Specification for a variety of reasons. Appropriate notation of sequences is now provided, as well as a Sequence Listing in both computer readable and paper formats. The Examiner notes that an Abstract is not provided on a separate page. The Applicant relies on the pamphlet for providing the required Abstract (see MPEP section 1893.03(e)) .

The Examiner has rejected Claims 1-9, 12-14, and 17 under 35 USC § 112, first paragraph for failing to enable the invention claimed. It is argued that "...the specification fails to disclose to one of skill in the art how to obtain the fragments embraced by the scope of the claims...". This information is, however, well known to those skilled in the art. The Applicants disclose relevant references in the Specification which describe the TnaA and trpR sequences (see Deeley and Yanofsky, (1981), and Gunsalus and Yanofsky, (1980)). What is more, it is clearly stated in the description that the TnaA sequence is modified so as to result in the loss of the tryptophanase activity. The biologically active fragments of the trpR are defined in the description as fragments which keep their repressor activity.

The Examiner also rejects Claims 1-21 under 35 USC § 112, second paragraph for failing to claim with particularity. The Examiner objects to the use of the language "all or part", but this language is defined in the Specification as all of the sequence of the promoter or the biologically active fragment of the promoter. This language provides one with skill in the art with sufficient

information to perform the claimed modifications. What is more, this sequence is defined numerous times in the Specification as being:
- the nucleic acid sequence which is capable of inactivating the gene...
- when said nucleic acid sequence (i.e. which is capable of inactivating the gene)...
- and integrating said sequence (i.e. which is capable of inactivating the gene)...
- sequence of a promoter...
- nucleic acid sequence encoding a molecule.

Thus, the Examiner will note that the Applicants have claimed with particularity. In each of the above instances the sequence is redundantly identified to avoid confusion.

The Examiner also requires confirmation that the gene encoding the protein of interest is in the same vector of the Ptrp promoter, and the Applicants hereby confirm this.

The Examiner rejects Claim 2 for the fact that the "method of Example 1 or 2" is claimed, but not included in the claim. The Applicants have deleted this language from the claim and explain that such chromosomal integration methods are well known in the art and not required in the claim.

The Examiner has requested that Claim 5 describe the nature of the "resolution" and "screening" steps. The Applicants respond that these steps are described in the publication Hamilton, Journal of Bacteriology, 171, 4617-1622 (1989) which is referenced in the Specification. This process is submitted to be known to those skilled in the art and consequently unnecessary in the claim.

Finally, the Examiner objects to the language "by any means" in Claim 6. The Applicants have amended the claim to better define the means of the claim.

Correct articles have been added to Claims 2, 6, and 10-17, as per the Examiner's request.

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With regard to prior art, the Examiner rejects Claims 1-11 under 35 USC § 103 for Obviousness citing the disclosure of Warne, et al., in view of Yanofsky, et al., for the reason that "...one of ordinary skill in the art would have been motivated to resolve strict repression of the overproduction system before induction which is important when using an expression vector with high copy number since inactivation of TnaA tryptophanase would result in increased production of the protein of interest." The Applicants respond that the instant invention is drawn to a method of expressing a protein under the control of a Ptrp promoter by transforming a cell with a vector encoding a nucleic acid sequence which is capable of inactivating the gene encoding a TnaA tryptophanase gene, a nucleic acid sequence encoding a molecule which acts negatively on the Ptrp promoter.

With regard to the Warne reference, the Applicants agree that it fails to teach a method for inactivating TnaA tryptophanase. However, the Applicants disagree that Warne teaches a plasmid vector wherein a Ptrp promoter is operably linked to the trpR gene. What is disclosed is a plasmid in which the trpR promoter is replaced with a weak constitutive promoter; i.e., the Ptrp promoter is linked to the protein of interest and not to the Ptrp. What is more, the method of Warne does not improve, but rather reduces the expression of the protein of interest.

Thus, it is submitted that this reference teaches a different method to produce proteins of interest.

The Yanofsky reference teaches at Figure 1 that in Trp-induced expression, the Rho factor does not bind to RNP, therefore not resulting in termination and thus not preventing the expression of TnaA. In contrast, the instant invention claims inactivation of the TnaA tryptophanase gene. Therefore, the prior art teach contrary to the instant invention. The Applicants note as well that the instant invention pertains to a vector encoding a nucleic acid sequence which is capable of inactivating the gene encoding a TnaA tryptophanase gene. Yanofsky does not even begin to suggest a nucleic acid sequence which is capable of inactivating the gene encoding the TnaA tryptophanase gene. Rather, Yanofsky simply discloses that Rho causes termination. The subject matter of the instant invention, namely inactivation of the gene encoding TnaA tryptophanase, cannot be considered to be obvious from the Yanofsky disclosure.

Finally, Yanofsky fails to teach the method for using a nucleic acid sequence encoding a molecule which acts negatively on the Ptrp promoter.

Thus, under the teaching of the CAFC in Ecolochem v. Southern California Edison Co., "The absence of a convincing discussion of the specific sources of the motivation to combine the prior art references, particularly in light of the strength of the prior art teaching away from [the instant invention], is a critical omission...". Ecolochem v. Southern California Edison Co., 56 USPQ2d 1065, 1075 (CAFC 2000). The Applicants have already pointed out the contradictions in both references, thus rebutting the *prima facie* Obviousness rejection. What is more, neither reference teaches a vector encoding a nucleic acid sequence which is capable of inactivating the gene encoding a TnaA tryptophanase gene.

The Examiner at the PCT international stage considered these references and found the instant invention novel and unobvious. In view of the above discussion, there can be no tenable grounds for maintaining the prior art rejection in this examination.

* * * * *

Accordingly, entry of the present amendment, reconsideration of all grounds of objection and rejection, withdrawal thereof, and passage of this application to issue are all hereby respectfully solicited.

It should be apparent that the undersigned attorney has made an earnest effort to place this application into condition for immediate allowance. If he can be of assistance to the Examiner in the elimination of any possibly-outstanding insignificant impediment to an immediate allowance, the Examiner is respectfully invited to call him at his below-listed number for such purpose.

Allowance is solicited.

Respectfully submitted,
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Enclosure: Postal Card Receipt,
Sequence listing, paper and computer readable, substitute specification pages 8, 15, 17, 18, 19, 20, and 25, and Statement under 37 CFR 1.821(f).

- 2 - (amended)

Method for producing a recombinant protein of Claim 1, in which the nucleic acid sequence which is capable of inactivating the gene encoding a TnaA tryptophanase is introduced into the DNA of the prokaryotic host cell [according to the chromosomal integration method described in Example 1 or 2].

- 6 - (amended)

Method for producing a recombinant protein of Claim 1, in which the induction of said promoter which is followed, in the 3' position, by a nucleic acid sequence encoding a molecule which is ribonucleotide or protein in nature, and which acts negatively on the Ptrp promoter or its transcription product is obtained by [any means enabling an inhibitory or activating effect to be exerted on said promoter] exerting on said promoter an inhibiting or activating effect.

- 10 - (amended)

A [F] first construct for transforming a prokaryotic host cell which can be transformed with a second construct for expressing a gene encoding a recombinant protein placed under the control of [the] a Ptrp tryptophan operon promoter in a prokaryotic host cell, wherein the first construct comprises a nucleic acid sequence which is capable of inactivating the gene encoding a TnaA tryptophanase when said nucleic acid sequence is introduced into said host cell.

- 11 - (amended)

The [F] first construct of Claim 10, wherein it also comprises, upstream of said nucleic acid sequence capable of inactivating the gene encoding a TnaA tryptophanase when said nucleic acid sequence is introduced into said host cell, all or part of the nucleic acid sequence of [the] a Ptna tryptophanase operon promoter.

- 12 - (amended)

The [F] first construct of Claim 10, wherein said nucleic acid sequence capable of inactivating the gene encoding a TnaA tryptophanase when said nucleic acid sequence is introduced into said host cell comprises a mutated fragment of the coding sequence of said TnaA tryptophanase.

- 13 - (amended)

The [F] first construct of Claim 12, wherein said mutated fragment is obtained by inserting a stop codon at a position such that the sequence of the mutated fragment thus obtained encodes a protein fragment lacking tryptophanase activity.

- 14 - (amended)

The [F] first construct of Claim 12, wherein said mutated fragment is a mutated fragment of the coding sequence of the TnaA tryptophanase of said host cell.

- 15 - (amended)

The [F] first construct of Claim 10, wherein said nucleic acid sequence capable of inactivating the gene encoding a TnaA tryptophanase when said nucleic acid sequence is introduced into said host cell is the nucleic acid sequence comprising all or part of the sequence of a promoter followed, in the 3' position, by a nucleic acid sequence encoding a molecule which is ribonucleotide or protein in nature, and which acts negatively on the Ptrp promoter or its transcription product.

- 16 - (amended)

The [F] first construct of Claim 15, wherein said promoter followed, in the 3' position, by a nucleic acid sequence encoding a molecule which is ribonucleotide or protein in nature, and which acts negatively on the Ptrp promoter, is all, or a part permitting promoter activity, of the Ptna tryptophanase operon promoter.

- 17 - (amended)

The [F] first construct of Claim 16, wherein said nucleic acid sequence encoding a molecule which is ribonucleotide or protein in nature, and which acts negatively on the Ptrp promoter, is the sequence encoding the TrpR tryptophan operon aporepressor or one of its biologically active fragments.